NCI Office of Cancer Centers Learning Series

NCI's Clinical Assay Development Program
transcript

Moderator: Melissa Glim
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Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen only mode. This conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the meeting over to Dr. Henry Ciolino. You may begin.

Henry Ciolino: Good afternoon. Welcome to the NCI's Office of Cancer Centers Learning Series. My name's Henry Ciolino, I'm a Program Director in the Office of Cancer Centers and I will moderate today's presentation. Today's topic is NCI's Clinical Assay Development Program. The goal of today's webinar is to familiarize you with the program and perhaps help you prepare a better application.

We have two presenters today. We are pleased to welcome Dr. Barbara Conley who is the Associate Director of the Cancer Diagnosis Program. That's in the Division of Cancer Treatment and Diagnosis of NCI. Dr. Conley's been in this position since 2010. Before that, she was a Senior

Investigator and Chief of the Cancer Diagnosis Program Diagnostics Research Branch here at NCI.

After Dr. Conley's presentation, we will be joined by Dr. Luke Utley of Agios Pharmaceuticals in Cambridge, Massachusetts. Dr. Utley is a Senior Scientist at Agios in Drug Metabolism and Pharmacokinetics Department.

A few housekeeping details: to see the slides of this presentation you'll need to have Microsoft Live Meeting installed on your computer. This will work best if you close all other applications on your computer. You will hear the audio part of the presentation by telephone at the number listed in the webinar invitation. You can't hear it through your computer. And you may use the question box to ask questions. Biographies of Dr. Conley and Dr. Utley as well as slides of this presentation will be available on the Office of Cancer Centers website following this webinar.

Dr. Conley, welcome. Please take us away.

Barbara Conley: Okay, thank you very much. It's a pleasure to be addressing whoever is out there and I'm going to talk to you a little bit about the clinical assay development program. This is a pilot program that we have been running for about a year now. And then Dr. Utley will give you some hint as to why they applied and how it's going for them, I hope.

So, why did we want to do such a program? The reason is because we had noticed - and I'm sure other people have noticed - that there's a lot of biomarker papers out there, but not very many of them are actually used to improve the treatment for cancer patients. And in our program, we are concerned with patients who are already diagnosed with cancers.

So this is not a situation where we're looking at early diagnosis or biomarkers of risk. But why are biomarkers studies not so successful, and that is because there's a lot of heterogeneity that one has to take into account, including the cellular, the tumor and the patient heterogeneity. Sometimes the biomarkers are measured by different assays and different places and these assay results may be variable within the same assay and certainly between assays there's variability as to how well they would detect the analyte of interest.

And then of course, another variability would be the specimens themselves. Many times these are conducted on specimens of convenience and so they don't have pre-analytic variables that are controlled. In other words, the specimens are collected however they were collected. They weren't collected for the purpose of the assay; storage and shipping could be variable. So, it ends up to be a lot of noise that blurs the marker and outcome correlation and validation, leading to frustration.

So, why did we decide to go with CADP? The Clinical Assay Development Program, as I said, is the pilot and we have supported clinical trials protocols in this division for some time and they often include markers that determine eligibility, stratification or treatment assignment. We term these *integral* markers. To date, the assays have rarely been validated to the point that they would meet clinical specifications for normal lab tests that you would order on any patient.

However, if we are to go forward into predictive markers, they have to be robust and the means to measure them in the clinic are urgently needed. Predictive markers would tell you which treatment might be more efficacious than another treatment. Also used are prognostic markers telling you which patients are likely to have worse prognosis or better prognosis than others.

A few definitions up front, analytical performance or analytical validity is how well does this test detect the analyte that you're interested in? How variable is it, what are the sources of variability and how can you best perform this test? Clinical validity is: does the result of the test correlate with your outcome of interest. In other words, if your outcome of interest is response, does this test correlate with response? Does it correlate with survival, or whatever your outcome of interest might be?

Other issues are clinical utility, which is if you have a validated assay and a provider uses this assay, can the outcome be better than it was by using whatever you're using now? Is it adding anything new to the current armamentarium? Assay qualification is often used as well and that's linking the biomarker with the biologic process or clinical endpoints to show that it is fit for purpose. The purpose could be toxicity markers or various other things, as well, as predictive or prognostic markers.

The Clinical Assay Development Program is not a grant. We take applications, but it is not a grant *per se*. It does provide resources, however; e.g., processes and services to efficiently develop diagnostic tests that address clinical needs, including the co-development of targeted agents and predictive markers. We wanted to develop clinical assays that do meet rigorous performance standards and also help speed the evaluation of molecularly guided treatment.

The components of the Clinical Assay Development Program are the Clinical Assay Development Network, and a specimen retrieval system. We have statistical expertise within the biometrics research branch in Doctors McShane and Polley. We have program expertise within the Cancer Diagnosis Program and we have project management with our Project Manager, Dr. Phillips

Rohan. On the slides, the star or the asterisks here are services for which we contract. I'll go into those a little bit now.

The Clinical Assay Development Network is a contract program. We basically had an application opportunity back in 2010 and CLIA-certified labs offered their expertise for consideration. The function of the laboratories is assay optimization and validation and production of standard operating procedures for the assay. These are CLIA certified labs and they're in the high level of CLIA certification so you would expect them to have procedures in place for assay platform such as chemistry, ELISA, ISH, RT-PCR and DNA sequencing.

We have eight contracts and one in-house molecular characterization laboratory that exists in NCI Frederick. These eight are at Dartmouth, MD Anderson, SeraCare, MolecularMD, University of Colorado at Denver, Oregon Health Sciences Center, University of Maryland and Midwest Research.

CADP has a specimen retrieval system, one of which is under a contract and others of which are more *ad hoc*. But the one that we have under contract is at Kaiser Permanente Northwest. It's a large health plan, it has stable membership, it has electronic records. That means that their storage of specimens from clinically diagnosed cancers over the last many years are connected to electronic health records and therefore are reasonably valuable as to availability of pathologic diagnosis and of clinical outcome data if you need it.

Now naturally for an assay development we don't need to know who these patients are and we would rather scrub all of their personal information except for the relevant information needed to validate the assay. And for that we use

a natural language processing tool developed at Harvard, which is almost totally accurate. The rest is done by hand to scrub the identifiers.

The Clinical Assay Development Program has certain submission dates and these are available on the Web site that'll be at the end of this presentation. And as you can see, we tried to have the site open for submission for at least four, five, six weeks and if you just look at the application receipt date, the SEP means Special Evaluation Panel. This lists their evaluation meetings and that I'll go into that a little bit later. We then have an internal committee and a senior advisory committee. But just to look at the February 15th date, we hope to be through with all of the evaluations to tell people whether or not they are accepted into the program between February and June. It's a very aggressive timeline that we try very hard to meet. Most of the time we meet it, but there are other issues that can get in the way such as material transfer agreements, things like that. But, at least for the evaluation, I think, we have a pretty good timeline.

Now what do you need to get into this program? Not much. You do have to have some kind of working prototype assay that works in human tissue similar to the tissue you propose to use for your assay. And importantly, the intended clinical use for the assay must be clearly defined. Prevalence data is very helpful. Not everyone will have the prevalence data but they should have some idea what the prevalence of this analyte would be in the population. And if you have any preliminary clinical validation data (that is does the result of the test correlate with the outcome that you're looking for), that's very helpful as well.

So, once you get into the program you might need to transfer to a quality environment. Let's say you have an assay that works in your research lab but you don't know what it will do in the CLIA validation situation. So, a "quality

environment" may be necessary in order to use the assay for a clinical trial. We need to know the analytic performance in the intended use context. In other words, patients will have the assay done one at a time not - on say 100 patients at a time. But when you do the assay in a clinical trial you're going to get one or a few patients at a time. So you need to know that the assay will work in that environment. You need to set preliminary cut points sometimes, so that needs to be a validation activity. And then assessment of clinical validity can be done in a retrospective specimen set if that is a well-designed study.

So, as you can see here on the right side of this slide, post discovery. You might need some consultation with the expertise in the program; project management is very helpful to keep on your timeline. Matchmaking refers to situations where one might need matchmaking potentially with a diagnostics company or potentially with a clinical trial that might be using the assay that you're planning. Platform migration is sometimes needed; commonly we see something that works in frozen tissue but maybe people want it to work in paraffin because it's a little more practical. Optimizing the assay, development of standard operating procedures, finding specimens is often needed, calibrators, reference sets often are not available for the diagnostics we use now. And something that very helpful is some statistical consultation and advice.

Okay. So again, requirements - any working prototype assay. We've tried to make the bar relatively low in order to be able to help the most people. But a clearly defined intended clinical use for cancer prognosis or prediction of treatment efficacy is essential. However, if your assay is further along, it doesn't mean you're not eligible for the program. Those assays might need further optimization, transfer to a quality environment, migration of the platform, and any of these other things that are on this slide. And assistance

with transportability might be important if the clinical trial is such that assays will be run in more than one laboratory.

This is a iagram of the process. The application is submitted, the special emphasis panel [Outside experts] meets to review and recommend suitable assays for the program. Outside Internal review at NCI is done to make sure that we have the resources that are necessary to support the assay and the assay is reasonably consistent with our strategic plans. A Senior Advisory Committee actually approves the funding. Resources are obtained through these contracts that we have. A Project management team is formed and then the project is started. I'm going to talk a little bit about project management in a little bit.

On the Special Emphasis Panels, each round has different members. We have approximately two from industry. It could be anywhere from pharma with diagnostic experience to diagnostics industry. Several different fields of clinical research - surgery, medical oncologist, et cetera. One or two patient advocates are always on this panel, pathologists who are also laboratorians serve on these panels as are experienced clinical trials statisticians, sometimes from the NCI cooperative groups.

The applications are evaluated based on whether their hypothesis is sound and what kind of clinical utility can be envisioned for this assay. Is the assay feasible in the samples that will be available and for the purpose that is intended? What is the clinical need for this? Is this just another assay to do something we already have an assay for or is this a totally new clinical need or something that adds value to what we already have? And then, what is this path to clinical implementation envisioned by the applicant?

So once the assay receives support, contracts are put in place with specimens and also with the CLIA [ed: Clinical Laboratory Improvement Amendments] labs that we have in the Clinical Assay Development Network. And then the project management team is formed, and it consists of the assay submitters, the Clinical Assay Development Network lab that's involved (that wins the contract), and also some NCI personnel. Timelines, milestones and go-no-go decisions are decided and then once the assay has gone through its process and it is actually finished, the assay does goes back to the submitter. We do not ask for any assignment of IP [ed: intellectual property].

So currently, we've had 16 applications from 15 applicants. One of them applied again. One project is in management right now and you'll hear from Agios, they are the project in management. One is ready for its task order and actually is out and under discussion at this time and one is under consideration by the Senior Advisory Committee, two plan to resubmit, and we are working with several assay submitters to hone their assay submission.

Useful Web sites are listed on this slide. For the CADP itself, http://.cadp.cancer.gov and the Cancer Diagnosis Program. [**www.cancerdiagnosis.nci.nih.gov**]. You can probably get on the NCI website, put in cancer diagnosis program, and it will direct you there but this is the direct link.

Henry Ciolino: Well thank you very much Dr. Conley. Do we have any questions from the audience?

You have sixteen applications so far in the program and I think the number was about four of five of them that have gotten passed the initial stage. What have been the shortcomings of the other applications?

Barbara Conley: Yes, I think what the shortcomings have been, by and large, is the intended clinical use of the assay has not been well defined. Some of them actually have failed on feasibility, not that it's unfeasible totally, but our resources could not support it. But I think people do need help on deciding what their assay will do. And it's usually should be one thing, not three or four things.

Henry Ciolino: Question, are they looking at too many different cancer types? Do you want a specific cancer type? Is that part of the...

Barbara Conley: It is a little bit all over the place. Some people think that their diagnostic can fit different cancer types, but just like a drug that might fit different cancer types in order to get an indication, you need to pick one and work on that one.

Henry Ciolino: I see.

Henry Ciolino: This is, as you said, not a grant it's an application for services. Is there anything about the application that you think the - our audience needs to know how it differs from a grant and its approach?

Barbara Conley: Yes, the application goes in through a website called Proposal Central. Many grants also use that Web site so people may be familiar with it. It's not a very long application but I do encourage anybody to talk to program first before they put it in if they can because you may get some helpful hints. Part of the reason we're doing this is because it is not a settled area as to how to develop a diagnostic or whether it is the companion diagnostic or not. There are certain things that are not settled and it would behoove discussing the existing data with the people in the Cancer Diagnosis Program to determine how best to position this so that it can be successful. We are looking for a few good assays.

Henry Ciolino: Okay. And applicants do have a chance to do a single revision of the application or multiple revisions?

Barbara Conley: Well, definitely a single revision. If they have actually multiple areas where the assay may be useful, have thought of a few different uses - clinical uses - they could do multiple because they would each be different.

Henry Ciolino: So it'll be the same biomarker applied to different...

Barbara Conley: But for a different reason. Correct.

Henry Ciolino: All right. All right, well thank you very much. I'd like to bring online Dr. Luke Utley of Agios Pharmaceuticals. Luke, could you join the conversation.

Luke Utley: I can indeed.

Henry Ciolino: All right, if you would take us through your presentation please on *Developing an IDH Patient Diagnostic: Why Small Biotech Is Partnering with Big Government*.

Luke Utley: The title is somewhat tongue in cheek actually. I live up in New Hampshire and so I see a lot of politicians. So anyhow, so the first couple of slides are some that we've presented to potential investors at JP Morgan, so these are publicly cleared information. I'm going to talk to you about our IDH program or isocitrate dehydrogenase.

Now, Agios focuses on their cancer metabolisms; specifically things like the Warburg Effect, which has been known since the 1920s, that cancer cells will consume glucose at a very high rate and they do so in an anaerobic fashion.

And this represents a - basically a differential used pathway, something that's not used in most of the other cells in the body in cancer patients so it's a target that - basically it's a targeted opportunity. So in 2009, Agios published a paper on the IDH mutations where a pair of metabolic enzyme are mutated in cancers - IDH1 and IDH2. And some genetic work validated at the target and multiple tumors. IDH1 is in about 27,000 patients. IDH2 was identified in about 15,000 patients. And we see these in acute myelogenous leukemia and glioma. So this had a potential to be a unique novel target. And we had discovered a relationship between the obvious mutation and the endogenous metabolite to HG, which is 2-hydroxyglutarate. And we saw that as a potentially valuable biomarker -a way to identify patients potentially.

That especially, using in that second context, that gave us a chance to develop a clinical program that'll be very rapid. It would allow us to select patients for the mutation and rule - deselect those who might not benefit from the therapy. And this last one, the developing breakthrough medicine is the sort of stuff we tell investors all the time that "yes, we actually are working on this. And in fact, we do have programs that are moving happily towards the clinic for this."

So cancer-associated IDH1 mutations, so the - IDH produces alpha-ketoglutarate [KG] under normal circumstances, converts isocitrate to alpha-KG. The mutated version does not. In fact it's - it seems to be a loss of functions on not increasing alpha-ketoglutarate. And what scientists at Agios had found that in fact it produces this 2 hydroxyglutarate. And this aside from being a biomarker is actually a metabolite and a pro-oncogenic compound that in turn turns around and regulates the DNA and histone methylation, which causes epogenic regulation of certain gene transcripts.

So it's basically proto-oncogenic. But it also serves - or could serve potentially as a biomarker for identifying patients. So we actually part of the program that we have running with NCI has two prongs to it. One is a more traditional CLIO-based type sequencing program to identify patients with the - either IDH1 or IDH2 mutation. The other is a not-so-traditional program where we're validating an assay for 2-hydroxyglutarate, which if you're not familiar with this compound, it's a very small, very hydrophilic molecule that's pretty difficult to analyze.

But what we've seen in some preliminary work was that levels of 2-hydroxygluderite in plasma seemed to correlate well with the patient's mutation status above a particular concentration level. The patient seemed to be almost 100% likely to have the IDH1 or 2 mutation, so, one of theories was that we could use this as a way to include patients in the trial with a simple bio-linearity method using plasma. And also hopefully use it as a marker of effect.

So the next slide. So we had done some proof of concept work with specific IDH1 and IDH2 inhibitors where we had engrafted IDH1 or IDH2s, specific tumors, into mice and then treated with these 2 different inhibitors. And what you can see is that at 75 and 150 mg/kg, we see a dose-dependent reduction in the 2HD production. So we saw profound, sustainable inhibition. And it - and the inhibition correlator with drug exposure.

So this was part of our proof of - or target proof of concept or proof of validation. And what got us thinking that, "hey, maybe we can also use this as a biomarker, hopefully for effect." I think you've already heard some about what makes a successful application. And since we're accepted into it, I guess we were a successful application. So that we came into this with what we feel was a fairly solid therapeutic hypothesis.

We also have some pretty in-depth knowledge of very novel biology and pharmacology mechanism of actions. And we have - we're partnered up with some of the premier experts in the field of cancer metabolism. And we came up with a pretty clear strategy for patient selection and the clinical pathway for our biomarker monitoring. We wanted to do both sequencing and monitoring of the plasma 2HG levels and then our proof of concept is that it seem to indicate that knocking down 2HG correlates with knocking down the tumor growth.

So we had a - we'd already done some pretty clinical pharmacology studies and those of - I can't show them to you, but basically they've gotten better as we've improved the compounds in that relationship has held up. So we had also a research-grade biomarker (assay for 2HG that we had developed in conjunction with the contract laboratory. And we hadn't done any validation other than just some very simple linearity accuracy and precision.

We're definitely not ready to go into clinical use. But we had something to at least start with that we can handover to the partner labs with NCI saying "well, here's a starting point." There weren't starting from scratch. And we already had cross-functional plan timeline for how the IND [ed: investigational new drug] and the clinical trials might run. So you know why choose NCI and NIH partner? Some of these things are probably pretty obvious. But others you know might not be.

I mean why would - and people here do call it a grant - although I've been told it's not. But you know why would apply for this sort of thing? Well, probably the obvious - the most obvious one is the access to the expertise. I mean NCI and the NIH have a network of disease area and diagnostic experts that you know are hard to find anywhere. I mean even in large pharma. And

for a company like Agios, you know we're pretty small, that's just absolutely invaluable to be able to you know have that on tap.

Also, the interface with the FDA, I mean, since our biomarker program is a little outside the box and it's fairly new, it would be nice to have an idea of what the FDA thinks of this before we go up for a formal review. And so we've been able to have some of those discussions especially with people who had that experience already and not just the "here's the website of you know whom to speak with at the FDA," but actually, "you should call this person."

So that's really been you know of great help in terms of facilitating the program with us. And sample access, you know, obviously the NCI is unique in that it's a central hub for a number of clinicians. And especially for oncology, that's where we're able to plan a clinical program where we can get a lot of samples from a lot of places that might not otherwise work with a small biotech.

And then of course budget. It's - this is something that because the funding is coming from outside, it makes good sense for us because our budget's limited. So before going to the next slide, I'm going to tell you a little about Agios that you might not be aware of.

So we are in large part a virtual company. We have pretty much our synthesis, our first line testing. And a lot of our heavy lifting biology is done with contract labs.

We keep the - basically the nitty gritty of the biology in house. But everything else is outside. So we have probably a good half dozen contract labs that we use on a regular basis and then a number of smaller specialty ones. So this was basically some advice that I give to people that would be going into this kind

of project because you will be working a CRO [ed: contract research organization]. And we found sometimes through creativity, sometimes through pure dumb luck the keys for success with working with those CRO partners.

And the first of them is having very clear objectives. And that's one nice thing about NCI programs is that it's the objectives are established at the beginning. You know, a document that everyone has. And it's pretty clear as what we're trying to get developed. And that definitely helps to keep things on track. Regular communication. I mean it sounds kind of obvious. But we asked to be appraised of everything, success and failure.

And the counterpoint for that is we don't beat people up for bad luck. I mean somebody trips and drops a plate you know, okay things happen. Now this was something that early on in the project we kind of ran into, so in the statement of work, we had scheduled monthly meetings. That's regular, but not quite regular enough. So we actually added because it's hard to diagnose problems on a 30-day sort of cycle.

So we asked can we have a smaller, much more focused meeting with just myself, one of the of the people from the laboratory side of things and the project coordinator on a weekly basis to try and see if there are any problems, let's get them solved then. And that actually has been very successful. I mean some of those meetings are very quick - just "yes, you know these are the things we had said we were going to do last time. They're on track. They're being done. Or they've been delayed for this reason, we'll have it in tomorrow" sort of thing.

When problems come up, we were able to solve them very quickly. So that's definitely something I would suggest for other participants in the program.

That you might want to have a little more - make sure you have the very regular meetings. Even if you end up just calling in and saying, "we don't have anything new on this. Scratch it." So we worked very hard to engage our CRO partners. And this is especially true when you're doing as much work outside of the organization as we do.

We really do treat them as partners. When I choose a CRO, it's based on their expertise. So it really makes sense for me to use that. I don't know everything in my field. And I don't think anyone does. So if there's somebody who has years of expertise in a particular, you know assay system or a particular area of regulation, I would be a fool not use that. Plus, when people are interested in what in what you do, when they feel engaged, they tend to go the extra mile.

Now that does mean that occasionally we're going to have disagreements. You know if I'm asking someone their opinion, they may tell me something I don't like. But I'd much rather hear that than just everyone comes nodding and going along and watching as I drive something off a cliff. We find a lot of value in person-to-person relationships. And this is something I would actually suggest for the NCI that perhaps this part of when projects start up, this sort of thing can be scheduled.

A chance to meet the people that are going to be doing the work, even if it's you know just very briefly or you know is done by Skype or something like that. Being able to put a name to a face has a lot of value. I mean we go to the trouble of flying our scientists to the contract labs in China that we use so that they can - really to be able to put a name to that person's face. So that later when we're having these teleconferences or email exchanges, I know who it is I'm really working with. I know something about them.

My default is always to try to go to teleconferences because email, it's just too easy to - you say something the wrong way or you write something in the wrong way; it gets misinterpreted. And the last thing really is flexibility. And this goes both ways. I mean biotechs, things change very, very, very rapidly from day to day. And we you know ask of our partners that they need to be able to accommodate that.

So one thing with the NCI, the work we've been doing that we've been able to accommodate those changes. But it's been a little slower just because of the paperwork process that goes on. So that's a little bit of feedback that I would give. But generally, it has been very been pretty darn flexible in terms of being able to accommodate issues as they've come up. I mean an example is that we went into this project wanting to be able to look at 2HG levels in the brain.

We really didn't know what the background levels of 2HG in human brain tissue were. And it's not a - it's not a matrix you can get terribly easily. And as we started getting tissue samples and then some preliminary archive patient samples, what we found was that our initial estimates were completely off. And the background levels were considerably higher. And the patient samples were an order of magnitude higher than that. So we ended up having to change the statement of work and game plan in terms of how we were going to analyze the samples and really what kind of utility they we're going to have.

And we try to remind ourselves here at Agios that this - like I said, this goes both ways. That there is this thing called reality in timelines. And that we can't be terribly rigid in things that we throw out there and demand from our partners.

So I think that is pretty much my last slide. I hope that tells you something about our experience to date with the program and provides some useful feedback for it.

Henry Ciolino: Well thank you very much doctor. I have a couple of questions for you. How - how did you approach preparing the application to the CADP? What were - what were the initial steps?

Luke Utley: That's actually not something that I can answer because it happened about a month before I joined Agios. So I would have to grab someone else and -

Henry Ciolino: That's okay. What specifically did you get out of the CADP, out of the program?

Luke Utley: Well so far we've been, like I said, we've been working on the validation of the bio-analytical plasma assay and for the sequencing essay. One of the main things that we've really gotten out of it has been the connection to a number of the cancer centers that are serving as I guess clearing houses for samples. And so we've done a little bit of work on patient samples locally here with places like MGH [ed: Massachusetts General Hospital]. Or we seem to see a correlation between the mutation status and the circulating levels of 2HG.

But that's a pretty limited number of samples. And we need to really see does that translate out to other patient populations. And make sure it's not something that just is an artifact of being in the patient population that's in the Boston area.

Henry Ciolino: But...

Luke Utley: That's something we're really look forward to.

Henry Ciolino: Did you actually get patient samples to work on? Were other labs involved in validating the assay?

Luke Utley: That was in the early days when we were doing the proof of concept work.

Henry Ciolino: Okay.

Luke Utley: And we had a research grade assay. So it's not something that I would submit to the FDA at all. We were really just looking to see is there - is there some correlation or is it just complete, you know is it completely random. I mean what we saw was a pretty strong one. But again, this was a couple of samples here, a couple of samples there. The big part of the program is going to be you know looking at things from multiple other centers.

Henry Ciolino: And your application was specific for gliomatosis? Is that correct?

Luke Utley: We have glioma and AML.

Henry Ciolino: We have a few questions for Dr. Conley. What sort of assays have you seen in the initial applications, ELISAs, IHCs, that sort?

Barbara Conley: I think we've seen them all almost. Seen some IHSs, PCR, ELISAs.

Henry Ciolino: Okay.

Henry Ciolino: Would the CADP provide any assistance in obtaining serum samples to try say a promising biomarker in liver cancer? Is that...?

Barbara Conley: Yes. Serum samples are a challenge for us as they're a challenge for everybody. If we thought the assay was one we're going to be supportive of and needed to be support, I think that's one of the issues we would have to go after as to feasibility. We could we find someplace that had these serum samples because they're not going to normally exist.

Henry Ciolino: And the funding you award doesn't go to the applicant *per se*. It's going to services.

Barbara Conley: Correct.

Henry Ciolino: Is that correct? Okay.

Henry Ciolino: Well we have one other question about FDA - help with FDA and interface with FDA. Is that anything? Luke mentioned that it was nice to tap into people that have expertise in dealing with them. But I just wondered as part of the application, is the FDA involved at all?

Barbara Conley: FDA is involved in the internal evaluation.

Henry Ciolino: Okay.

Barbara Conley: You know if you see that diagram that we have, we have someone from the CDRH's devices [ed: Center for Devices and Radiological Health], *in vitro* devices, on that panel. And in addition, we have frequent conversations with the device people at the FDA. And increasingly so with CDER, the Center for Drug Evaluation Research, so what - what is currently going on is that the FDA would love to approve novel drug with their companion diagnostics at the same time.

That means that not only do you have to get your drug information together for the investigational new drug application and the NDA, you also need the assay validation information if you have a companion assay. And this is what Agios is mentioning. They had an assay that worked as research grade. But if they want to come in with this drug, they will need a companion assay. That kind of validation needs to go forward in a way that can be acceptable to the FDA.

Luke Utley: Yes. And our current plan right now is that at some point to go to the FDA kind of on a provisional basis and you know lay our cards on the table and say, "well this is what we're - what we've been working on." I mean they've been involved in certainly in a proposal in the - in that was submitted but also you say "well this is where we've gotten - how does this look to you. You know, what's your initial reaction to this?"

And you know, hopefully it will be positive. And it won't be people's hair standing on end. But you figure it's best you know to go in and have that conversation initially. And get some feedback and change things before the official submission and before we get too deep into it.

Henry Ciolino: Okay.

Barbara Conley: So...

Henry Ciolino: We have a question on...

Barbara Conley: Yes.

Henry Ciolino: Is there a cost to acquire specimens for industry specimens?

Barbara Conley: Yes. I'm not sure exactly what - what that question refers to. But if a project is accepted, there's no cost to the submitter for the specimens. Maybe that clarifies it.

Henry Ciolino: Okay. And we also have a question. I know we have - you have a due date of June 15 is the next one? Is that correct?

Barbara Conley: Yes.

Henry Ciolino: And does the website provide information about the format of the application?

Barbara Conley: Yes.

Henry Ciolino: Good. Alright. One more question.

Barbara Conley: Yes.

Barbara Conley: The question is does the FDA have a list of markers they think need additional validation that we can collectively work on? Not that I know of. I think they're pretty much on the receiving end. Although internally in the program, we might have - we've talked a little about, you know, is there some way to say, "well, okay we need markers for this and should we send it out to the community to work on."

But there's no - we haven't come to a conclusion on that.

Henry Ciolino: Well I'd like to thank our presenters, Dr Utley and Dr. Conley.

Barbara Conley: Thank you.

Henry Ciolino: Thank you.

Barbara Conley: All the information about this can be found on the website and that is cadp.cancer.gov. Finding all your information there. If you don't find it, call us.

Henry Ciolino: And you have our - an email address for Dr. Conley on the screen right now as well as the URLs for a variety of NCI sites including CADP. And I'd also like to remind everybody that NCI's Cancer Information Service offers comprehensive research-based information in English and Spanish for patients, the public, health care professionals and cancer researchers. And contact information is on the screen. [1-800-4-CANCER, www.cancer.gov/livehealp, or cancergovstaff@mail.nih.gov]

I thank you all for joining us today. And I hope you found it informative and useful.

Coordinator: Thank you for participating on today's conference. The conference has concluded. You may disconnect at this time.

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